

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Jost-Price et al.	Confirmation No.:	8006
Serial No.:	10/670,488	Art Unit:	1617
Filed:	September 24, 2003	Examiner:	Sahar Javanmard
Customer No.:	21559		
Title:	METHODS AND REAGENTS FOR THE TREATMENT OF DISEASES AND DISORDERS ASSOCIATED WITH INCREASED LEVELS OF PROINFLAMMATORY CYTOKINES		

DECLARATION OF GRANT ZIMMERMANN, PH.D.

I declare:

1. I am an inventor of the subject matter that is described and claimed in the above-captioned patent application. I hold the position of Vice President, Discovery Sciences and Technology, for the assignee of record of the application, CombinatoRx, Inc.
2. I have read and understood the Office Action that was transmitted in connection with the above-captioned patent application on September 4, 2008.
3. Under my supervision, the majority of combinations of an immunosuppressive agent and an antidepressant described in Siegel were tested using an *in vitro* TNF α secretion/production assay similar to the assay described in the specification at page 78, lines 14-28. Using this assay, we have demonstrated that several different combinations of a glucocorticoid and a SSRI act synergistically to suppress the secretion/production of TNF α . For example, data for the combination of prednisolone and paroxetine indicate a

synergistic decrease in the secretion/production of $\text{TNF}\alpha$ (Exhibit 1). Using the same assay, we have found that the majority of the 800 combinations of an immunosuppressive agent and an antidepressant disclosed in Siegel demonstrate no activity or synergy. For example, theobromine has no effect on $\text{TNF}\alpha$ secretion/production when administered alone, and also shows no combination effect with prednisolone (Exhibit 2).

4. We have found that synergy with a glucocorticoid is a rare event. Using the above described $\text{TNF}\alpha$ secretion/production assay, we have tested 858 combinations of a glucocorticoid and a secondary agent. These data were assigned a synergy score, with a higher numerical score representing a greater synergistic effect for the tested combination of agents. The vast majority of the tested combinations (Exhibit 3; "Historical GC-Combos") showed no synergy above that observed for "the drug with itself" (Exhibit 3; "Self-Crosses"). The glucocorticoid combinations disclosed by Siegel, exclusive of the combinations with SSRIs (Exhibit 3; "Siegel Excl Act SSRI"), show only subtle differentiation from the "drug with itself" pairings, and are considerably less synergistic than the glucocorticoid/SSRI combinations (Exhibit 3; "GC Act SSRI Combos").

As only 12 combinations, or 1.5% of the total 800 different combinations of an immunosuppressive agent and an antidepressant described in Siegel are directed to glucocorticoid/SSRI combinations, one would not reasonably predict a synergistic effect for all the combinations of an immunosuppressive agent and an antidepressant described in Siegel.

5. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable

by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Date:

3/4/2009

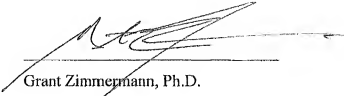

Grant Zimmermann, Ph.D.

Exhibit 1

Inhibition (%)

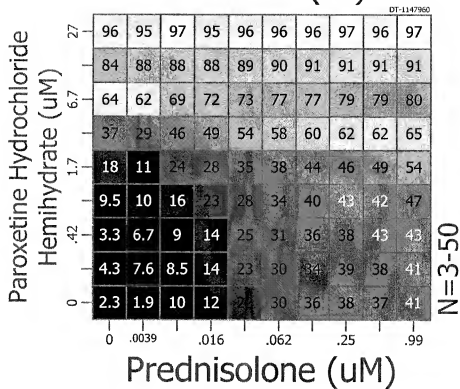


Exhibit 2

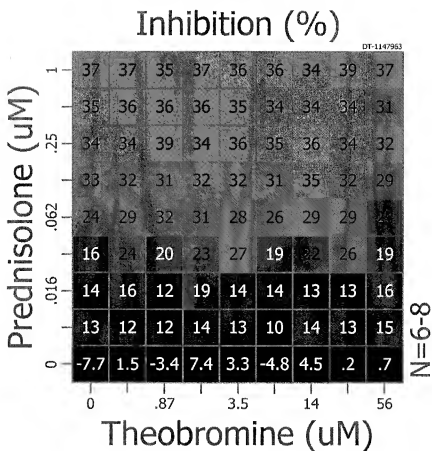


Exhibit 3

